Results: Over a median follow-up of 45 months, 250 patients (50%) experienced disease progression after treatment, 49 (10%) developed distant metastases, 20 (4%) died from prostate cancer, and 21 (4%) died from other or unknown causes. The 4-year progression-free probability (PFP) was 45% (95% confidence interval [CI], 40%–50%). By multivariable analysis, predictors of progression were Gleason score of 8 to 10 (hazard ratio [HR], 2.6; 95% CI, 1.7–4.1; $P < .001$), preradiotherapy PSA level greater than 2.0 ng/mL (HR, 2.3; 95% CI, 1.7–3.2; $P < .001$), negative surgical margins (HR, 1.9; 95% CI, 1.4–2.5; $P < .001$), PSA doubling time (PSADT) of 10 months or less (HR, 1.7; 95% CI, 1.2–2.2; $P = .001$), and seminal vesicle invasion (HR, 1.4; 95% CI, 1.1–1.9; $P = .02$). Patients with no adverse features had a 4-year PFP of 77% (95% CI, 64%–91%). When treatment was given for early recurrence (PSA level ≤2.0 ng/mL), patients with Gleason scores of 4 to 7 and a rapid PSADT had a 4-year PFP of 64% (95% CI, 51%–76%) and of 22% (95% CI, 6%–38%) when the surgical margins were positive and negative, respectively. Patients with Gleason scores of 8 to 10, positive margins, and receiving early salvage radiotherapy had a 4-year PFP of 81% (95% CI, 57%–100%) when the PSADT was longer than 10 months and of 37% (95% CI, 16%–58%) when the PSADT was 10 months or less.

Conclusions: Gleason score, preradiotherapy PSA level, surgical margins, PSADT, and seminal vesicle invasion are prognostic variables for a durable response to salvage radiotherapy. Selected patients with high-grade disease and/or a rapid PSADT who were previously thought to be destined to develop progressive metastatic disease may achieve a durable response to salvage radiotherapy.

Commentary

The most effective and appropriate management of biochemical relapse following radical prostatectomy is a matter of much debate. Although previous investigators have suggested that isolated, local recurrence is uncommon after such surgery, this study suggests otherwise. Sixty-seven percent of patients achieved a complete response to radiation therapy and the 4-year progression-free probability was 45%. Furthermore, the study demonstrated that some patients whose cancers had features typically associated with distant disease, such as Gleason Grade 8 to 10 and a rapid PSA doubling time, had a durable response to radiation, especially if associated with a positive surgical margin. It should also be noted that the dose of radiation given in many cases may have been considered subtherapeutic by many so response rates could have been higher. In addition, this study was not designed to show that such therapy, even when effective, has an impact on disease-specific survival rates. Although not a randomized trial, physicians may want to rethink their patterns of care for such patients based on this study.

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Phase I trial of yttrium-90–labeled anti–prostate-specific membrane antigen monoclonal antibody J591 for androgen-independent prostate cancer. Milowsky MI, Nanus DM, Kostakoglu L, Vallabhajosula S, Goldsmith SJ, Bander NH, *Division of Hematology and Medical Oncology, Department of Medicine, Weill Medical College of Cornell University, New York, NY.*

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Purpose: To determine the maximum-tolerated dose (MTD), toxicity, human antihuman antibody (HAHA) response, pharmacokinetics, organ dosimetry, targeting, and preliminary efficacy of yttrium-90–labeled anti-prostate-specific membrane antigen monoclonal antibody J591 (^{90}Y-J591) in patients with androgen-independent prostate cancer (PC).

Patients and Methods: Patients with androgen-independent PC and evidence of disease progression received indium-111-J591 for pharmacokinetic and biodistribution determinations followed 1 week later by ^{90}Y-J591 at five dose levels: 5, 10, 15, 17.5, and 20 mCi/m^2. Patients were eligible for up to three re-treatments if platelet and neutrophil recovery was satisfactory.

Results: Twenty-nine patients with androgen-independent PC received ^{90}Y-J591, four of whom were re-treated. Dose limiting toxicity (DLT) was seen at 20 mCi/m^2, with two patients experiencing thrombocytopenia with non-life-threatening bleeding episodes requiring platelet transfusions. The 17.5-mCi/m^2 dose level was determined to be the MTD. No re-treated patients experienced DLT. Nonhematologic toxicity was not dose limiting. Targeting of known sites of bone and soft tissue metastases was seen in the majority of patients. No HAHA response was seen. Antitumor activity was seen, with two patients experiencing 85% and 70% declines in prostate-specific antigen (PSA) levels lasting 8 and 8.6 months, respectively, before returning to baseline. Both patients had objective measurable disease responses. An additional six patients (21%) experienced PSA stabilization.

Conclusion: The recommended dose for ^{90}Y-J591 is 17.5 mCi/m^2. Acceptable toxicity, excellent targeting of known sites of PC metastases, and biologic activity in patients with androgen-independent PC warrant further investigation of ^{90}Y-J591 in the treatment of patients with PC.

Commentary

Prostate-specific membrane antigen (PSMA) is an excellent target for monoclonal antibody imaging and therapy because of its expression in high grade, metastatic and hormone-refractory prostate cancer [1,2]. In addition, it is not secreted like PSA or PAP. J591 is an anti-PSMA monoclonal antibody that binds tightly to the extracellular domain of PSMA. This is a significant improvement over previous monoclonal antibodies, which bound to an intracellular domain, available only in dead or dying cells. Toxicity in the current trial was consistent with that seen in other studies of ^{90}Y-labeled monoclonal antibodies and was mainly hematologic in nature. Two of the 29 patients with advanced

androgen-independent disease had significantly measurable responses. Six had stable serum PSA profiles. Importantly, 81% of bone and soft-tissue lesions were accurately targeted. This trial, showing acceptable toxicity, good targeting and evidence of biologic activity, suggests that additional investigation is warranted using different radionuclides, attachment of chemotherapeutic agents, and various trial designs.

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Laboratory Research

Platelet-derived growth factor receptor inhibitor imatinib mesylate and docetaxel: a modular phase I trial in androgen-independent prostate cancer. Mathew P, Thall PF, Jones D, Perez C, Bucana C, Troncoso P, Kim SJ, Fidler IJ, Logothetis C., *Department of Genitourinary Medical Oncology, Unit 427, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX.*

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Purpose: To study the platelet-derived growth factor receptor (PDGFR) inhibitor imatinib mesylate in androgen-independent prostate cancer (AIPC), alone and in combination with docetaxel, we designed a modular phase I trial. Our goals were to [1] evaluate the toxicity and maximum-tolerated dose of docetaxel with imatinib, and [2] evaluate the decline of prostate-specific antigen (PSA) induced by imatinib alone, and imatinib and docetaxel.

Patients and Methods: Twenty-eight men with AIPC and bone metastases were enrolled to receive imatinib 600 mg daily lead-in for 30 days, then imatinib 600 mg daily and one of six possible doses of docetaxel weekly for 4 weeks every 6 weeks.

Results: During the imatinib lead-in module, one dose-limiting toxicity (DLT) event was observed, while two (7%) of 28 had PSA decline (both <50%). With imatinib and docetaxel, cycle 1 DLT was found in three of 12 patients at docetaxel 30 mg/m^2, in three of four patients at docetaxel 45 mg/m^2, and in five of six patients at docetaxel 35 mg/m^2. DLTs (n = 40 total events) were principally fatigue (35%) and nausea (20%). Eight (38%) of 21 had PSA decline greater than 50%, and six (29%) of 21 had PSA decline less than 50%. Serial PSA declines beyond 18 months were observed. PDGFR-expressing tumor declined on serial bone marrow biopsies with combination therapy alone.

Conclusion: With imatinib 600 mg daily, the maximum-tolerated dose of docetaxel was determined to be 30 mg/m^2 weekly for 4 weeks every 6 weeks. Long-term responses were observed. The role of imatinib in modulating outcomes to docetaxel in AIPC is being tested in a randomized phase II trial.

Commentary

Imatinib (Imatinib Mesylate, STI571, or Gleevec™) is a small molecule tyrosine kinase inhibitor with established clinical activity in CML and GIST. Imatinib functions through competitive inhibition at the ATP-binding sites of tyrosine kinases. Imatinib has demonstrated preclinical activity in cell lines that express bcr-abl, the c-Kit receptor, and the platelet-derived growth factor (PDGF) receptor. PDGF receptor inhibition may result in activity against tumors such as breast cancer, prostate cancer, lung cancer, ovarian cancer, sarcoma, and gliomas. Combining imatinib with cytotoxic chemotherapeutic agents in the treatment of solid tumors might have particular advantages. Imatinib is known to modulate cytotoxic agent delivery to tumor cells, by decreasing the interstitial pressure and increasing the capillary to interstitium transport of selective drugs. This is mediated by inhibition of PDGF beta receptors expressed in blood vessels and stromal cells but not in malignant cells [1]. Increased capillary transport of chemotherapeutic agents can lead to enhanced antitumor activity. Because doceatxel has established activity in prostate cancer, combining imatinib with docetaxel may lead to enhanced antitumor activity based on the modulation of stromal cells and vascular endothelial cells by imatinib.

The above report combines weekly docetaxel with daily imatinib, and this regimen elicited a >50% PSA decline in 38% of the patients (n = 28). Notably, all the patients were heavily pretreated, with many of them having been previously treated with taxanes. Currently, this weekly regimen is being tested in the Phase II setting in chemo-naïve patients with AIPC. In another Phase I study [2], a total of 29 patients with advanced solid tumors were treated with daily imatinib and docetaxel every 3 weeks. The recommended Phase II (RP2) dose of this combination is: imatinib 400 mg po qd + docetaxel 60 mg/m^2 IV q 3 weeks. At this dose the combination is well tolerated, with pharmacokinetic analyses, revealing no drug-drug interaction. In this report almost half of the patients had AIPC, with equal numbers of chemo-naïve and chemo-refractory patients. In contrast to the first report, none of the taxane refractory patients (n = 6), had a PSA response to the q 3 week regimen. However, six of seven taxane-naïve patients had a >50% PSA response to this regimen, with a prolonged duration (3–9 months). Although the numbers of patients with AIPC were relatively small in both the studies, collectively these reports suggest that the combination of imatinib and doceatxel maybe useful in selected subsets of patients with AIPC.

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